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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER
JOYCE, CATHERINE

ART UNIT	PAPER NUMBER
1642	

DATE MAILED: 10/13/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/821,203	SIDRANSKY ET AL.	
	Examiner	Art Unit	
	Catherine M. Joyce	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *11 July 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-24* is/are pending in the application.

4a) Of the above claim(s) *15-22* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-14 and 23-24* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

1. The Amendment filed July 11, 2006 in response to the Office Action of January 13, 2006 is acknowledged and has been entered. Claims 1-24 are pending, claims 15-22 are withdrawn from consideration as being drawn to a non-elected invention, and claims 1-14 and 23-24 are under examination. Applicant's illumination of the fact that claims 23 and 24 should have been rejoined in the previous Office Action is acknowledged and claims 23 and 24 are hereby rejoined and examined.

2. The text of those sections of Title 35, U.S. Code not included in this Action can be found in a prior Office Action.

3. The following rejections are being maintained:

Claim Rejections - 35 USC § 112

4. Claim 10 remains rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement as set forth on page 3, paragraph 7 of the paper mailed January 13, 2006.

Applicant argues that claim 10 has been amended to recite that the human whose blood is being tested is suspected of having a thyroid neoplasm and thus the result of the test is likely to be relevant to the thyroid neoplasm and not to a second tumor in another part of the body. Applicant further argues that no diagnostic or prognostic test is 100% accurate and the PTO does not require 100% accuracy for enablement of a diagnostic or prognostic method, and that the standard for enablement presents a reasonable number of inoperatives or false positive results.

These arguments have been considered but have not been found to be persuasive. In the first aspect, Applicant argues limitations not found in the claims in that the claims are not drawn to a method of identifying an individual likely to have a malignant thyroid neoplasm but are rather drawn to a method of distinguishing

malignant from benign thyroid samples. In the second aspect, Applicants arguments that the standard for enablement permits a reasonable number of inoperatives or false positive results is not found to be persuasive because, as set forth in the previous Office Action, a substantial number of non-thyroid cancers including melanoma, colon carcinoma, head and neck cancers, and lung cancers exhibit the specified mutation. Thus, given the large number of other cancers that contain the specified mutation of a T to A transversion at nucleotide 1796 of BRAF, it appears that the number of likely false positive results is not a reasonable number.

New Grounds of Rejections

Claim Rejections - 35 USC § 112

5. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

6. Claims 23-24 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite. The term "higher risk" in claims 23 and 24 is a relative term that renders the claim indefinite. The term is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention.

7. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

8. Claims 1-10 and 23-24 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method for distinguishing

malignant papillary thyroid neoplasms from benign thyroid neoplasms comprising determining the presence of a T to A transversion at nucleotide 1796 of BRAF according to SEQ ID NO:1 in a thyroid papillary neoplasm sample of human, wherein presence of the transversion indicates a malignant papillary neoplasm and absence of the transversion indicates a benign papillary neoplasm, does not enable a method for distinguishing malignant from benign thyroid samples comprising determining the presence of a T to A transversion at nucleotide 1796 of BRAF according to SEQ ID NO:1 in a thyroid sample of human, wherein presence of the transversion indicates a malignant neoplasm and absence of the transversion indicates a benign neoplasm or sample. This means the thyroid neoplasm may have any morphology.

The factors to be considered in determining whether undue experimentation is required are summarized In re Wands 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988). The court in Wands states: "Enablement is not precluded by the necessity for some experimentation such as routine screening. However, experimentation needed to practice the invention must not be undue experimentation. The key word is 'undue,' not 'experimentation.' " (Wands, 8 USPQ2d 1404). Clearly, enablement of a claimed invention cannot be predicated on the basis of quantity of experimentation required to make or use the invention. "Whether undue experimentation is needed is not a single, simple factual determination, but rather is a conclusion reached by weighing many factual considerations." (Wands, 8 USPQ2d 1404). The factors to be considered in determining whether undue experimentation is required include: (1) the quantity of experimentation necessary, (2) the amount or direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims.

The claims are drawn to the following:

a method for distinguishing malignant from benign thyroid samples comprising determining presence of a T to A transversion at nucleotide 1796 of BRAF according to

SEQ ID NO:1 in a thyroid sample of human, wherein presence of the transversion indicates a malignant neoplasm and absence of the transversion indicates a benign neoplasm or sample (claim 1),

wherein the thyroid sample is a fine needle aspirate (claim 2),

wherein the thyroid sample is a tissue sample (claim 3),

wherein the thyroid sample is a cytological sample (claim 4),

further comprising providing a diagnosis based on the presence or absence of the transversion (claim 5),

further comprising providing a prognosis based on the presence or absence of the transversion (claim 6),

further comprising determining a therapeutic regimen for the human using as a factor the presence or absence of the transversion (claim 7),

wherein the thyroid sample is a tissue sample, wherein the sample has a papillary follicular morphology (claim 8),

wherein the thyroid sample is a tissue sample, wherein the sample has a papillary morphology (claim 9),

further comprising providing a prognosis based on the presence or absence of the transversion, wherein the presence of the transversion indicates a higher risk of neck lymph node metastasis (claim 23),

further comprising providing a prognosis based on the presence or absence of the transversion, wherein the presence of the transversion indicates a higher risk of cancer recurrence (claim 24),

and

a method for distinguishing malignant from benign thyroid samples, comprising: determining presence of a T to A transversion at nucleotide 1796 of BRAF according to SEQ ID NO:1 in a blood sample of a human, wherein presence of the transversion indicates a malignant thyroid neoplasm in the human and absence of the transversion indicates a benign neoplasm or no neoplasm (claim 10)

The specification teaches that discloses methods for distinguishing malignant from benign thyroid samples wherein the presence of a T to A transversion at nucleotide 1796 of BRAF indicates a malignant thyroid neoplasm and the absence of the transversion indicates a benign neoplasm in the sample (paragraph 08). The specification further teaches that BRAF mutation was found in papillary thyroid tumors having the papillary classic morphology, the papillary follicular morphology, and the tall cell morphology but not in follicular cancer, Hurthle cell cancer, and medullary cancer (Table 1).

The specification cannot be reasonably extrapolated to enable the scope of the claims because one of skill in the art could not predict that the method of the invention would function as claimed in distinguishing malignant thyroid from benign thyroid neoplasms for other than malignant papillary thyroid tumors because the specification clearly demonstrates that the only thyroid malignancies that present with a T to A transversion at nucleotide 1796 of BRAF are malignant papillary thyroid tumors. In particular, as set forth above, the specification specifically teaches that the cited BRAF mutation is not found in thyroid neoplasms that are follicular cancer, Hurthle cell cancer, and medullary cancer. Thus, one of skill in the art could not predict and would not expect to be able to distinguish any thyroid malignant neoplasm from a benign thyroid neoplasm, other than a malignant papillary thyroid tumor, using the instantly claimed method.

Thus, given the teaching in the art and the lack of guidance with regard to this issue such as by way of working examples, one of skill in the art could not predict that

the invention would function as claimed. Thus, practice of the invention would require undue experimentation

9. If applicant were able to overcome the rejection of claims 6 and 23-24 under 35 U.S.C. 112, first paragraph, as recited above, claims 6 and 23-24 would still be rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method for distinguishing malignant from benign thyroid samples comprising determining presence of a T to A transversion at nucleotide 1796 of BRAF according to SEQ ID NO:1 in a thyroid sample of human, wherein presence of the transversion indicates a malignant neoplasm and absence of the transversion indicates a benign neoplasm or sample, does not reasonably provide enablement for said method further comprising providing a prognosis based on the presence or absence of the transversion.

The claims are as follows.

a method for distinguishing malignant from benign thyroid samples comprising determining presence of a T—A transversion at nucleotide 1796 of BRAF according to SEQ ID NO:1 in a thyroid sample of human, wherein presence of the transversion indicates a malignant neoplasm and absence of the transversion indicates a benign neoplasm or sample, further comprising providing a prognosis based on the presence or absence of the transversion (claim 6),

wherein the presence of the transversion indicates a higher risk of neck lymph node metastasis (claim 23),

wherein the presence of the transversion indicates a higher risk of cancer recurrence (claim 24).

The specification teaches as set forth above. The specification further teaches that 28/54 (55%) of BRAF+ patients showed lymph node as compared to 14/69 (20%) of BRAF- patients and that 9/54 (55%) of BRAF+ patients showed cancer recurrence as

compared to 3/69 (20%) of BRAF- patients. The specification also teaches that a recent study on a large Japanese series of PTC with similar number of cases as instantly studied (Namba et al., 2003, J. Clin. Endocrinol. Metab. 88(9)L4393-7) showed no significant association of BRAF mutation with extrathyroidal invasion and lymph node metastasis (page 10). The specification also teaches that the relationship of the BRAF mutation with other known risk/prognostic factors remains to be clarified in larger studies (page 10).

The teaching of the specification cannot be extrapolated to enable the scope of the claims because one of skill in the art could not predict that the invention would function as claimed. In particular, Tockman et al (Cancer Res., 1992, 52:2711s-2718s) teach considerations necessary in bringing a cancer biomarker to successful clinical application. Although the reference is drawn to biomarkers for early lung cancer detection, the basic principles taught are clearly applicable to the use of the BRAF mutation for the prognosis of thyroid cancer. Tockman et al teaches that prior to the successful application of newly described markers, research must validate the markers against acknowledged disease end points and confirm marker predictive value in prospective population trials (see abstract). Tockman goes on to teach that markers have clear biological plausibility and **if validated** (emphasis added) can be used for population screening (p. 2713s, col 1). The essential element of the validation of a marker is the ability to test the marker on clinical material obtained from subjects monitored and to link those marker results with subsequent clinical confirmation of, in the instant case, cancer recurrence and neck lymph node metastasis. Clearly, prior to the successful application of newly described markers, markers must be validated (p. 2716s, col 2). Given the teaching in the art that cancer markers must be validated and given the teaching in the specification on the discrepancy between studies with regard to the prognostic value of the BRAF mutation in thyroid cancer and the suggestion in the specification that the relationship of the BRAF mutations with other prognostic factors remains to be clarified with larger studies, one of skill in the art could not predict that the

invention would function as claimed. Thus, practice of the invention would require undue experimentation.

Claim Rejections - 35 USC § 102

10. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

11. Claims 1, 3, 4, and 9 are rejected under 35 U.S.C. 102(a) as being anticipated by Kimura et al. (April 1, 2003, Cancer Research 63:1454-1457).

The claims are drawn to the following:

a method for distinguishing malignant from benign thyroid samples comprising determining presence of a T—A transversion at nucleotide 1796 of BRAF according to SEQ ID NO:1 in a thyroid sample of human, wherein presence of the transversion indicates a malignant neoplasm and absence of the transversion indicates a benign neoplasm or sample (claim 1),

wherein the thyroid sample is a tissue sample (claim 3),

wherein the thyroid sample is a cytological sample (claim 4),

wherein the sample has a papillary morphology (claim 9).

Kimura et al. teaches that an analysis of 124 snap-frozen thyroid tumor samples including papillary carcinomas showed that the BRAF-V599E mutation (resulting from a transversion at nucleotide 1796) was found only in papillary thyroid carcinomas, and not in benign or malignant follicular neoplasms (pages 1454-1455). Thus, all of the claim limitations are met.

Claim Rejections - 35 USC § 103

12. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

13. Claims 2, 5 and 7 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kimura et al. (April 1, 2003, Cancer Research 63:1454-1457) in view of Tyler et al. (1994, Surgery 116(6):1054-60) (abstract only).

The claims are as follows:

a method for distinguishing malignant from benign thyroid samples comprising determining presence of a T—A transversion at nucleotide 1796 of BRAF according to SEQ ID NO:1 in a thyroid sample of human, wherein presence of the transversion indicates a malignant neoplasm and absence of the transversion indicates a benign neoplasm or sample (claim 1),

wherein the thyroid sample is a fine needle aspirate (claim 2),

further comprising providing a diagnosis based on the presence or absence of the transversion (claim 5),

further comprising determining a therapeutic regimen for the human using as a factor the presence or absence of the transversion (claim 7).

Kimura teaches as set forth above, but does not specifically thyroid samples that are fine needle aspirates or providing diagnoses or determining therapeutic regimens in bases on the presence or absence of the transversion.

Tyler et al. teaches that fine needle aspirates are used for thyroid cancer diagnosis and that the majority of invasive cancers are found in patients whose lesions are suspicious for papillary carcinoma, and that the risk of carcinoma in these subgroups warrants early surgical intervention.

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to substitute the thyroid sampling technique of Tyler for the sampling method of Kimura because the technique is not invasive and success using the technique would have been reasonably expected because of the demonstrated

success of the technique in Tyler. Further, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to combine the teaching of Kimura with the teaching of Tyler to provide a diagnosis and determine a therapeutic regimen based on the detection of the transversion. One of skill in the art would have been motivated to combine the teachings because of the teaching in Tyler of the risk of invasiveness of papillary carcinomas and the recommendation of early intervention surgery in such cases. One of skill in the art would have had a reasonable expectation of success in the combination because of the demonstrated success of Tyler in using the transversion to distinguish malignant and benign samples.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Catherine M. Joyce whose telephone number is 571-272-3321. The examiner can normally be reached on Monday thru Friday, 10:15 - 6:45.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jeffrey Siew can be reached on 571-272-0787. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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